

obviousness-type double patenting as obvious in view of claims 15-21 of copending U.S.S.N. 09/973,419. These rejections are respectfully traversed.

Dull teaches homologs of the instantly claimed compounds where the carbon adjacent to the methyl amine group is a methylene group. Dull does not disclose or suggest compounds with any substitution at this position. Applicants enclose a Declaration under 37 C.F.R. § 1.132 of William S. Caldwell, which distinguishes the claimed compound from the compounds disclosed by Dull.

#### **Declaration under 1.132**

In his Declaration, Dr. William Caldwell outlines several important differences between compounds with a methylene (the Dull patent) or a methyl substituent (as presently claimed) at a position alpha to the amine group. The differences relate to the biological and pharmacokinetic characteristics of the compounds, including their high affinity for the receptor and ability to elicit functional response at the receptor and resistance to metabolic clearance.

As stated in the Declaration, in light of problems associated with the metabolism of the N-methyl-4-(3-pyridinyl)-3-buten-1 amine compound described in the Dull patent, an effort was made to identify compounds that possessed both good binding/functional characteristics and good pharmacokinetic profiles. Several attempts were made to vary the substituent at the 5-position of the pyridine ring of N-methyl-4-(3-pyridinyl)-3-buten-1 amine. For example, the substituent at the 5-position of the pyridine ring was varied, but while these compounds retained binding at  $\alpha 4\beta 2$  receptor (as evidenced by their  $K_i$  value), they did not solve the metabolism problem. The results, and the isolation of metabolites, indicated that the problem might involve monoamine oxidase activity at the secondary amine side chain.

Next, substitutions were made at other positions on the N-methyl-4-(3-pyridinyl)-3-buten-1 amine compound. For example, a single methyl group was added to the 2-position of the pyridine ring, the 6-position of the pyridine ring, or to the amino group, and an N-isopropyl derivative was also prepared. These substitutions resulted in dramatically reduced binding characteristics.

Next, Applicants investigated compounds including an  $\alpha$ -methyl group. These compounds showed improved metabolic characteristics and retained binding at the  $\alpha 4\beta 2$  receptor. The  $\alpha$ -methyl group is believed to create a degree of steric hindrance, relative to the unsubstituted material, which hinders binding at the oxidase active site. The compounds have an improved overall combination of biological and pharmacokinetic characteristics (high affinity for the receptor, ability to elicit functional response at the receptor and resistance to metabolic clearance). These characteristics make the claimed  $\alpha$ -methyl compounds significantly better drug candidates than the unsubstituted analogs described in the Dull patent.

The other methyl derivatives that were evaluated are also homologs of the N-methyl-4-(3-pyridinyl)-3-buten-1 amine compound described in the Dull patent. It would have been just as obvious to make these substitutions as it would be to make the claimed substitution, yet only the claimed substitution resulted in compounds with the improved properties. Given the relatively unfavorable effect of similar substitution at other positions, this result was unexpected and should be considered to render the claimed compound non-obvious in view of the prior art. Accordingly, withdrawal of the obviousness and obviousness-type double patent rejections over the Dull patent is respectfully requested.

With respect to the remaining obviousness-type double patenting rejection, co-pending U.S.S.N. 09/973,419 has not yet been allowed. Applicants will file a terminal disclaimer, as appropriate, upon an indication of allowance in this and/or in the other application.

The Examiner is invited to contact the undersigned if he has any questions or further comments.

Respectfully submitted,

A handwritten signature in cursive script, appearing to read "David S. Bradin".

David S. Bradin

Reg. No. 37,783

Attorney for Applicant

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Womble Carlyle Sandridge & Rice, PLLC

Post Office Box 725388

Atlanta, Georgia 30358-2601

Telephone: (919) 484-2382

Facsimile: (919) 484-2380